

## SPECIFICATION

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**TITLE:**       **PREMIXED CALCIUM PHOSPHATE CEMENT PASTES**

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### **CROSS REFERENCE TO RELATED APPLICATION**

This is a utility application based upon provisional application Serial No. 60/263,894 filed January 24, 2001 entitled "Premixed Calcium Phosphate Cement Pastes" for which priority is claimed.

## BACKGROUND OF THE INVENTION

This development was supported in part by USPHS Research Grant DE11789 to the American Dental Association Health Foundation from the NIDCR. The United States or an agency hereof may therefor have certain rights to the claimed invention.

A self-hardening calcium phosphate cement, consisting of tetra calcium phosphate (TTCP) and anhydrous dicalcium phosphate has been shown in clinical studies to be efficacious as a bone repair material. The hardening time (HT) of the cement is about 30 min when the powder constituents are mixed with water and 5 min when mixed with a phosphate solution as the liquid. Hydroxyapatite (HA) is the major product formed as a result of the mixing and hardening. In recent years, additional calcium phosphate cements (CPC) that do not contain TTCP have been developed, e.g.  $\alpha$ -tricalcium phosphate (TCP) and  $\text{CaCO}_3$ ; dicalcium phosphate (DCPA) and  $\text{Ca}(\text{OH})_2$ . These cements harden in 10 min when mixed with a phosphate solution, and they also form HA as the final product.

A cement paste of the type referenced mixed with glycerol was studied for root canal filling, sealing, and injectability and it was reported that the glycerol-calcium phosphate cement (CPC) paste showed better biocompatibility than a number of presently used root canal filling or sealing materials. However, the prior art did not teach a paste material useful as a bone cement that remains stable over a period of time and hardens only when delivered to a desired site.

## SUMMARY OF THE INVENTION

The present invention comprises compositions and means for formulating premixed glycerol and calcium phosphate cement pastes that are stable in a package, resist washout, and

will harden only after being delivered to the defect or implant site. Glycerol was used as the liquid because the CPC hardening reaction to form HA does not occur in a water-free environment. Hydroxypropyl methylcellulose (HMC) and  $\text{Na}_2\text{HPO}_4$  were also added to improve the paste cohesiveness and accelerate cement hardening upon delivery to a desired repair site.

### DESCRIPTION OF THE PREFERRED EMBODIMENT

TTCP was prepared by heating an equimolar mixture of commercially obtained DCPA and  $\text{CaCO}_3$  at  $1500^\circ\text{C}$  for six hours in a furnace and then quenched in air or inert gas to room temperature. Also, TCP was prepared by heating a mixture that contained 2 mol of DCPA and 1 mol of  $\text{CaCO}_3$  to  $1200^\circ\text{C}$  for six hours followed by quenching to room temperature. The powders used were ground individually in a planetary ball mill in cyclohexane, ethanol, or dry to obtain the desired median particle size which is about 15 microns and as disclosed in the prior art for making CPC powders.

Nine liquids containing glycerol and various amounts of HMC (in powder form) and  $\text{Na}_2\text{HPO}_4$  (in powder form) were then prepared. Their compositions, expressed as mass fractions (%) of HMC and  $\text{Na}_2\text{HPO}_4$ , are shown in Table 1. The CPC-I, - II and -III were an equimolar mixture of (1) TTCP and DCPA; (2)  $\alpha$ -TCP and  $\text{CaCO}_3$ , and (3) DCPA and  $\text{Ca}(\text{OH})_2$ , respectively. CPC pastes were prepared by mixing the prepared CPC powder with the liquid glycerol mixture at powder-to-liquid ratios of 3.5 to 1 to 1.8 to 2.2 and 1.5 to 1.8, respectively. Diametral tensile strength (DTS) samples were prepared by placing the paste into molds (6 mm diameter x 3 mm height) with  $\approx 2 \text{ MP}_a$  of pressure applied. The DTS samples were kept in a mold covered with two fritted glass slides and immersed in a physiologic-like solution (PLS)

[1.15 mM Ca, 1.2 mM P, 133 mM NaCl, 50 HEPES, pH = 7.4] at 37°C Glycerol-PLS exchange occurred through the fritted glass allowing the CPC to harden. Samples were removed at 4 hours, then immersed in PLS for an additional 20 h. A Universal Testing Machine (United Calibration Corp, Garden Grove, CA, USA) measured DTD values at a loading rate of 10 mm/min. The Gilmore needle method measured HT. Powder X-ray diffraction analysis (XRD) determined the extent of CPC conversion to HA.

All pastes had excellent washout resistance, they remained stable and hardened while immersed in PLS. The HT and the DTS of 24 hour samples are shown in Table 1. The Newman-Kuels multiple comparison test indicated that the Na<sub>2</sub>HPO<sub>4</sub> amount, not the HMC amount, significantly (P < 0.05) affected the DTS and HT. Within each group of HMC amount for CPC-I, the lowest phosphate amount substantially increased the DTS while the highest phosphate amount dramatically reduced the HT. For samples CPC-II and -III, the highest phosphate amount significantly increased the DTS and decreased the HT. X-ray diffraction showed only partial conversion of CPC-I to HA and complete conversions of CPC-II and -III to HA in the 24 hour samples.

Table 1. Na<sub>2</sub>NPO<sub>4</sub> and HMC compositions expressed as mass fraction (%) in glycerol, 24 h DTS and HT.

Liquid	Na <sub>2</sub> NPO <sub>4</sub>	HMC	DTS(MPa)	HT(Min)
<b>CPC-I</b>				
L1	7.5	0.55	4.1(0.4)	111(6)
L2	15	0.55	2.8(0.2)	93(3)

Liquid	Na <sub>2</sub> NPO <sub>4</sub>	HMC	DTS(MPa)	HT(Min)
L3	30	0.55	2.1(0.2)	62(2)
L4	7.5	1.1	4.2(0.2)	97(8)
L5	15	1.1	2.6(0.1)	92(3)
L6	30	1.1	2.6(0.3)	63(3)
L7	7.5	2.2	3.6(0.6)	97(6)
L8	15	2.2	3.2(0.3)	93(3)
L9	30	2.2	2.3(0.3)	62(3)

#### **CPC-II**

L1	7.5	0.55	2.0(0.4)	117(3)
L2	15	0.55	2.5(0.2)	107(3)
L3	30	0.55	3.4(0.4)	80(5)

#### **CPC-III**

L1	7.5	0.55	0*	>420
L2	15	0.55	1.0(0.2)	170(5)
L3	30	0.55	1.5(0.1)	125(5)

Numbers in parentheses denote standard uncertainty (n = 4 and 3 for DTS and HT, respectively).

\* Not measurable.

The premixed CPC pastes would generally have a longer hardening time and lower physical strength, but the results suggest that cement pastes with excellent washout resistance can be prepared by incorporating HMC and Na<sub>2</sub>HPO<sub>4</sub> in glycerol. Phosphate generally

decreased HT and DTS for CPC-1, and increased DTS for CPC-II and -III. HMC appeared to decrease HA formation for CPC-I, but had no effect for CPC-II and -III, and did not affect DTS.

In sum, formation of a bone replacement or dental replacement paste results by combining dry powder constituents, characterized by their conversion to HA in the presence of water or phosphate solutions, with glycerol and hydroxypropyl methyl cellulose and/or  $\text{Na}_2\text{HPO}_4$ . The ratio of combined constituents is broad and the resulting paste can be formulated to control rather precisely, the hardening times. Glycerol compounds, analogs and substitutes as well as cellulose analogs and substitutes are within the scope of the invention.

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